THE EFFECT OF MESCALINE ON DIFFERENTIATED CONDITIONAL REFLEXES [1]

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Experimentally produced neurosis in animals was first described by Pavlov(16, 17) in 1913-1922. Since then, this experimental or situational neurosis has been observed by many investigators using methods of conflicting conditional stimuli, excessive stimuli, or changes in other external factors(7).

However, one drawback in applying the results of these experiments to humans and clinical psychiatry is that these methods are not applicable to the production of artificial human neurosis. In order to draw a more fruitful analogy between human and animal psychopathology it is necessary to use a common method in producing experimental behavior disturbances in both species.

Mescaline is useful in this respect. Psychological effects have been described by many workers including Beringer(1), Zucker(26), Klüver(14), Stockings(23), and Guttman (10), and it has been the most widely used method of producing drug induced experimental neuroses and psychoses in humans. Some psychiatrists suggest that mescaline produces an intoxication rather than a real psychotic state even though this occurs with a clear sensorium. Recent studies by Hoch (11, 12) and his collaborators have revived interest in its use as a psychiatric research tool. They found it produced schizophrenic-like symptoms in normal humans and accentuated the symptoms of schizophrenic patients. Among the psychological effects of mescaline, Hoch describes hallucinations, delusions of a paranoid, grandiose, or hypochondriacal nature, depersonalization experiences, disturbances of thought and negativism. These symptoms are accompanied by lack of insight and amnesia for the events. High doses produce catatonic reactions.

Vogel(24) describes mescaline's neurophysiological effects as mydriasis, flushing of the face, elevation of blood pressure, increased sweating, tremors, exaggerated tendon reflexes, occasionally clonus but no Babinski, and reduction of Alpha waves in the EEG with increased prominence of low voltage fast activities.

Biochemical and pharmacological studies on mescaline have been published. Quastel (18) noted that it depresses the normal oxidation processes and glucose metabolism of the brain. Grace(9) found it a depressant on the central nervous system. Its effect of lowering blood pressure was abolished if the vagi were cut or atropine administered. Mescaline's depressant effect in this regard seemed to be rather specific for the cerebral cortex since in decorticate cats it produced a rise in blood pressure. For anesthetized dogs small doses raised the cardiac rate while high doses slowed it. Recently Marrazzi and Hart(15) described mescaline's ability to produce an inhibition of the synaptic transmission. None of these studies, however, measured its effect on conditional reflexes.

Mescaline was administered to dogs by de Jong(13) who stated that it produced disturbances similar to negativism and catatonia. This was recently confirmed by Seevers(19). Among the disturbances described by de Jong were diminished motor initiative without paralysis, negativism as measured by resistance to change of position, the assumption of abnormal and bizarre postures, and particularly the maintaining of the front legs in a crossed position when placed that way. Thus in mescaline one has a common method of producing experimental neurosis in both animals and humans. We thought it exceedingly important to make a controlled study of the basic neurodynamic action of this drug, for, as Solomon(20) states, it is possible to assume that fundamentally the mechanism of origin of natural and experimental psychotic phenomena is a similar one.

Since the quantitative determination of conditional reflexes has been shown by Gantt (25) to be an accurate and controlled index

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of cerebral functioning, this method was employed in our study. Similar experiments on the action of alcohol, caffeine, bromide, chloral, amytal, benzedrine, and morphine have been already published (4, 6, 21, 22, 25).

METHOD

Our method has been described in detail by Gantt(7). The dogs were placed in an experimental camera which was designed to prevent stimuli other than the conditional stimuli from interfering with the tests. While the motor reflexes were measured, cardiac and respiratory rates were taken by means of an electrocardiograph and pneumograph. The conditional stimuli (CS) used were 2 tones produced by an audio-frequency oscillometer, T256 and T512, with an octave difference between them. The reflex studied was the defense or pain reflex which was produced by the unconditional stimulus, US (a faradic shock to the skin), which produced the unconditional reflex, UR, flexion of the foreleg and accompanying cardiac, respiratory, and general behavior changes. Both tones or signals lasted for 5 seconds. T256, which was always followed or reinforced immediately by the US or electric shock, became the positive or excitatory stimulus, and T512, which was never reinforced, became the negative or inhibitory stimulus as differentiation developed. The flexion of the foreleg during the CS and the accompanying cardiac, respiratory, and behavioral changes were observed as conditional reflexes, CR's. A stable level of response was established with regard to the following variables: the general behavior of the animal; the character of the subcortical orienting reflex; the latent period of the conditional reflex (the time between the CS and the CR); the amplitude of the CR; the amplitude of the UR; the percentage of correct motor reflex responses; and the percentage increase or decrease in the accompanying cardiac rate.

Four dogs were used; 2 had been used in our Pavlovian laboratory for other experiments and had well-established, stable defense reflexes. These were Skipper, a female mongrel 5 years old, weighing 17 kg., and having 1,000 repetitions of the CS, and Butch a very excitable male, 6 years old, weighing 14 kg., and having 400 repetitions of the CS, and good differentiation after 75 of them. Two other dogs were procured from the pound for this study and a stable level of conditional reflexes had to be initially established. These were Chow, a male mongrel, age 2, fairly excitable, who had 375 repetitions of the CS with differentiation after 180 of them, and Rocky a 2-year-old lethargic male mongrel who had 375 repetitions with differentiations after 100 of them. Chow, whose initial heart rate was 40/min. developed and maintained a heart rate of 180/min. on 375 repetitions of the CS. Experimental tachycardia had been observed previously in this laboratory by Dykman and Gantt(3).

All these dogs had 100% correct motor responses (always lifted their legs to T256 and never to T512) and obviously significant cardiac changes with T256. After 10 control records were collected and found to have little variance, different dosages of mescaline were administered and the effect noted. During the control period intramuscular saline was given so that any change occurring would be due to the mescaline alone and not to the injection procedure.

RESULTS

Results are listed in the accompanying table. The percent motor responses pertain to the incidence of foot flexions during the control and mescaline periods with 20 repetitions of the CS in each case. The percent cardiac change is the mean of the percent change of heart rate (increase or decrease) during 20 repetitions of the CS as compared with the 5-second period before the CS. Since the control percentages, which were recorded the day before the drug experiment, were the same as the measurements of the 200 preceding stimuli repetitions, we believe the marked change under mescaline is significant and is due to the drug and not the chance variance.

As shown in the table, the effect of mescaline varied with the dose. The drug was administered intramuscularly, which, according to Seevers (19), gives approximately the same plasma levels as intravenous administration. Hoch(11) used a dose of 7 mg/kilo i.v. in humans to produce schizophrenic-like symptoms. This dose in our dogs had little effect on the conditional reflexes except per-

haps to increase the size of the cardiac change. The dogs also began to exhibit a peculiar chewing motion that became marked with higher doses.

When the dose was increased to 35 mg/kilo definite changes appeared (Table 1). The motor responses were slightly diminished as measured by percent responses,

TABLE 1

Dog	Measurement	Control		Mescaline 7 mg/kilo		Mescaline 35 mg/kilo		Mescaline 70 mg/kilo	
		Excitatory T_{256} %	Inhibitory T_{512} %	T_{256} %	T_{512} %	T_{256} %	T_{512} %	T_{256} %	T_{512} %
CHOW									
	Withdrawal of foot to stimulus	100	0	100	0	90	0	0	0
	Cardiac rate change with CS	19	−7	28	−5	2	−4	−1.5	−5
	Cardiac rate change with US	24	—	23	—	12	—	3	—
ROCKY									
	Withdrawal of foot to stimulus	100	0	100	0	90	0	40	0
	Cardiac rate change with CS	20	4	28	5.3	3.3	1.6	−4.6	−1.4
	Cardiac rate change with US	38	—	28	—	15	—	9	—
BUTCH									
	Withdrawal of foot to stimulus	100	0	100	0	100	0	20	0
	Cardiac rate charge with CS	14	−4.5	21	−4	5.5	−6	−5.5	−6
	Cardiac rate change with US	9.3	—	15	—	16	—	7.5	—
SKIPPER									
	Withdrawal of foot to stimulus	100	0	100	0	80	0	0	0
	Cardiac rate change with CS	38	0	58	0	−2	−2.1	−2.5	−3.5
	Cardiac rate change with US	38	—	69	—	3	—	5	—

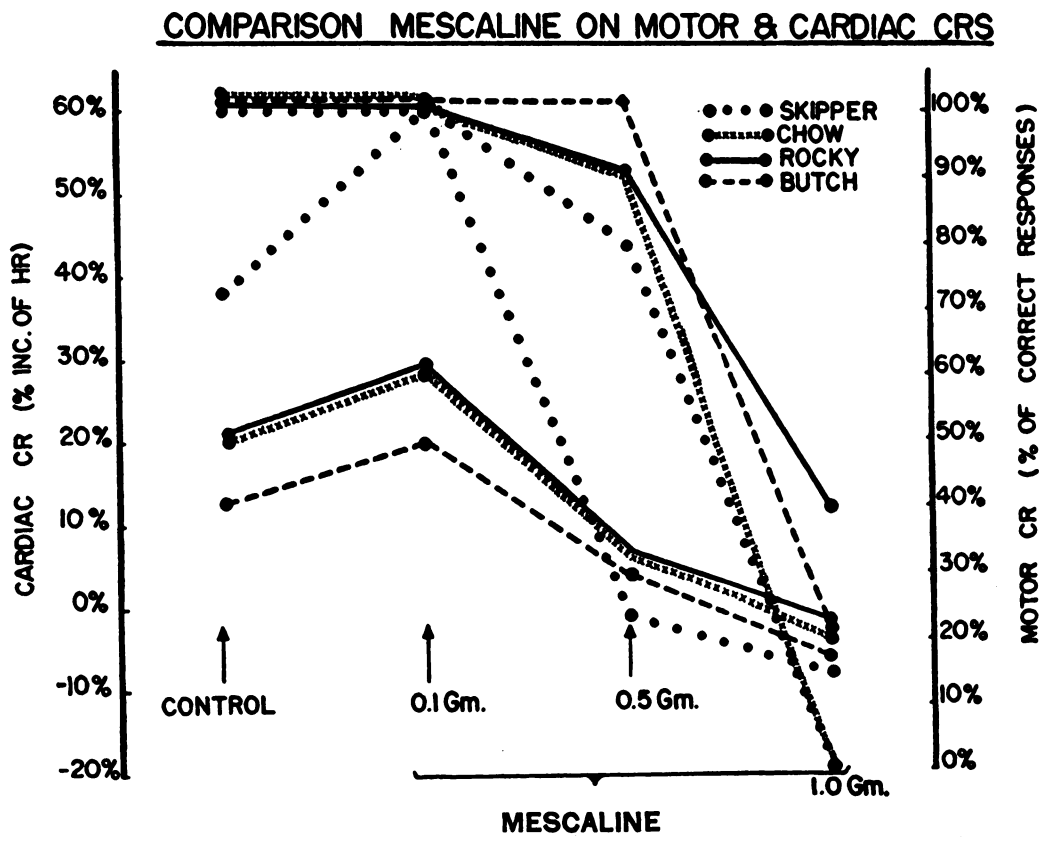

FIG. 1

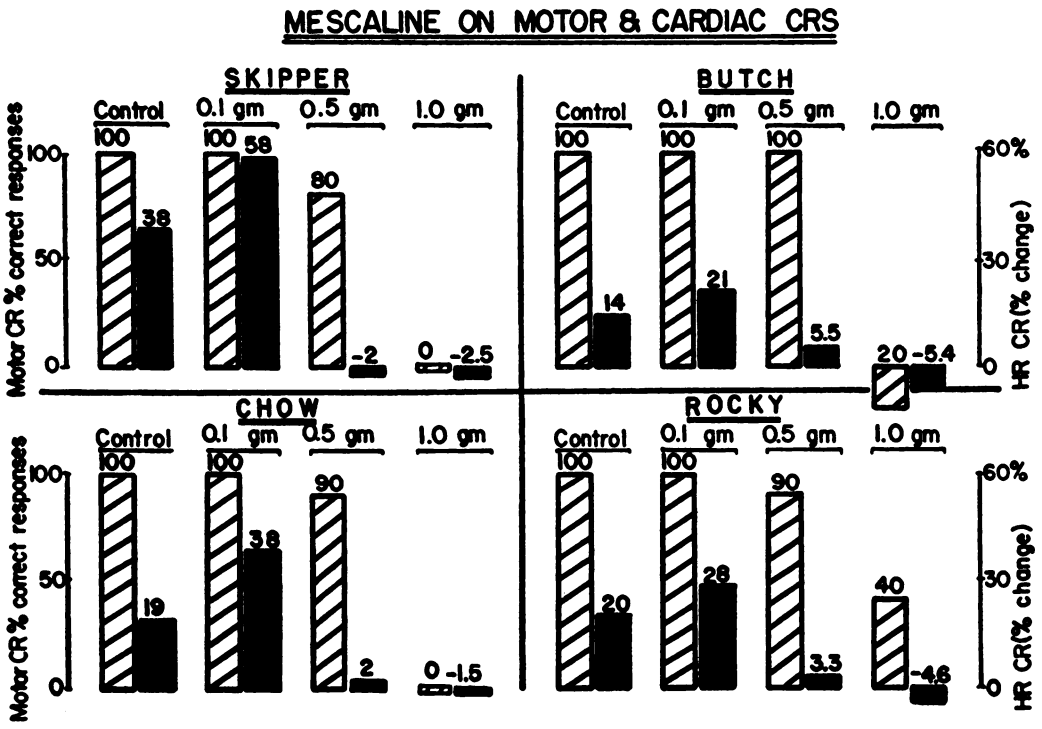

FIG. 2

decrease in amplitude, and increase of latent period. However, with this motor reflex relatively intact there was complete inhibition of the cardiac component of the excitatory conditional reflex. A split between motor and autonomic functions under morphine had been observed previously by Gantt(21, 22), but, under morphine, it was the motor response that was inhibited while the cardiac component remained intact.

In order to determine if the nature of the split was dependent on the character of the specific dog or the action of the specific drug, morphine was given to 2 of them. Under 5 mg/kilo of morphine, Skipper gave only 60% correct motor response but a 60% cardiac change. Rocky was given 4.6 mg/kilo of morphine and he gave only 20% correct motor responses while his cardiac change increased 42%. Thus the split under mescaline is directly opposite to that observed with morphine.

When the dose of mescaline was increased to 70 mg/kilo the conditional motor responses were also almost completely inhibited (Figs. 1 and 2); however, 2 dogs continued to give a small response. The unconditional cardiac reflex was also inhibited but the unconditional motor reflex, while diminished in amplitude, remained intact. The orienting reflex remained intact under all doses.

In respect to general behavior under the drug some very interesting phenomena were observed. During the control period 3 of the 4 dogs usually barked, howled, or yelped with the US or electric shock but rarely did so with the excitatory CS. However, under the effects of mescaline, they all began to squeal and howl with the T256, the excitatory stimulus, in the same manner as with the electric shock. These vocalizations were also recorded as changes in the respiratory reflexes on the pneumograph. Thus while the dogs did not give any motor or cardiac responses, they still showed 100% differentiation between the tones in that they howled and showed general emotional reaction with T256 while remaining very quiet with the T512. This howling with both the excitatory CS and the US did not occur under morphine.

Their lack of motor responses did not appear to be due to motor paralysis since they could easily run around the antecamera.

Among the behavioral disturbances noted was a state which has been described by de Jong(13) as similar to catatonia. The dogs would assume fixed bizarre positions with their hind legs rigidly extended and their heads bent low. They would remain in that posture for long periods as if in a trance and could be pulled *en masse* along the floor on all fours, a state which de Jong calls negativism. However, when finally coaxed to move, they ran fairly well in spite of some ataxia. A pan of water was brought to the mouth of one dog who drank insatiably. The pan was immediately removed and placed directly in front of him. He bent his head toward the pan and opened his mouth but never reached the water, remaining in that straining position for 10 minutes, although he showed no motor paralysis and was still thirsty since he drank eagerly when the pan was again lifted to his mouth. Other symptoms noted were mydriasis, peculiar chewing movements, hyperactive knee reflexes, and intact placing reflexes.

In respect to the inhibitory effect of mescaline on the conditional and unconditional cardiac reflex, it was not a direct action on the cardiac system alone, but seemed to be related to the animals' reaction to external stimuli; for in 3 dogs the general heart rate without stimuli rose some 25%, and in one it remained constant under mescaline.

Discussion

In this experiment mescaline produced a state of inhibition (the excitatory conditional reflexes were inhibited) as well as a quantitative dissociation or cleavage between the emotional (visceral) and superficial motor responses, the cardiac reflexes being abolished before the motor. This relation between inhibition and dissociation was noted in many instances by Pavlov(16, 17). He produced a state of hypnosis in his dogs by repeating inhibitory stimuli and observed a divergence between the secretory and motor components of the food reflex. The saliva began to flow when the food was given although no skeletal movements were made in the direction of the food, and the reverse was noted when the conditional salivary reflex disappeared, but the motor reflex to food and chewing remained normal. He also noted that under this state of inhibition or hypnosis the dogs manifested negativism and catatonic traits similar to those we found under mescaline. A dissociation or cleavage between the various systems that the animals use in responding to their environment was also found in neurotic dogs by Pavlov(16, 17) and Gantt(5, 8). This disharmony was called "schizokinesis" by Gantt(8) and postulated as one of the basic mechanisms underlying psychopathy. Pavlov(16, 17) thought that many symptoms of schizophrenia could be explained by a state of partial inhibition or hypnosis. The production of inhibition and schizokinesis under mescaline supports these 2 viewpoints.

One interesting phenomenon that occurred under mescaline was the manner in which this disorganization was manifested. Along with the inhibition of the motor and cardiac reflexes there occurred the accentuation of the "emotional" vocalizations during the conditional stimuli. These vocalizations were of the same quality as those exhibited with the unconditional stimulus. The dogs reacted to the CS tone as if it was the US or electric shock itself.

Based on this peculiar phenomenon, we suggest a neurodynamic hypothesis that under the inhibiting effects of mescaline and its resulting schizokinesis, the normal relations between CS and US are disturbed and the CS begins to have an effect on the animal as if it were the US—the signal for reality comes to act as if it were reality itself. Such dissociation in response appears to explain many of the symptoms seen in disturbed behavior.

Gantt(7) has described the ease of development of pathological CR's in neurotic animals. In normal dogs the CS has to be combined with the UR in order to become established as a CR. However, in neurotic dogs, any new or neutral stimulus has to be combined only with a CS for pathological behavior, and it itself then becomes a pathological CR. This development of disturbed behavior going on without the benefit of the original excitant has been called "autokinesis" by Gantt(8). The above-mentioned hypothesis may help explain the mechanism of this phenomenon. Each new pathological CS acts in the neurotic dog in a manner simi-

lar to the original traumatic US. Thus while reinforcing itself, it produces new pathological CR's from the neutral stimuli. In this way the behavior disturbance has almost unlimited possibilities of spreading to involve new organ systems and new aspects of the environment. Pavlov(16, 17) described neurotic dogs who had CR's that had a quality of pathological inertness—could not be extinguished by nonreinforcement. This may be caused by the conditional stimuli acting like unconditional stimuli and thus reinforcing themselves.

Before applying the results of this experiment to humans and their clinical syndromes, we mention Pavlov's(16, 17) theory concerning the higher nervous activity of human beings. He felt that, in common with animals, humans had UR's (inborn reflexes or instincts) plus primary conditional reflexes formed from a first system of signals of reality (such as sensations, perceptions, or direct concrete impressions of their environment). In addition, he believed that human beings have a second system of signals of reality including speech, ideas or verbal thoughts, generalizations and abstractions. These are the "signals of the first signals" of the above-mentioned primary system. Pavlov states that direct impressions of objects and phenomena of the external world are the first signals of reality and that the verbal symbols or verbal designations of these direct impressions are the second signals of reality. Normally the first and second signal systems are in harmonious interrelationship with one another.

In our laboratory mescaline administered to dogs produced a disorganization of the normal relations between the CS and the US, and we postulated that the CS began to act in a manner similar to the US. Extending this hypothesis to human beings it is possible that mescaline produces a disharmony or schizokinesis of the normally coordinated 3 systems of highest nervous activity—the unconditional or inborn reflexes and the first (CR) and second (verbalization) signal systems. Furthermore, with the production of disorganization, just as the primary CS comes to stand for the more primitive US in dogs, in humans the secondary system of words, ideas, abstractions, and generalizations comes to act like the more primitive, primary CR system of concrete perception of stimuli. Thus verbal concepts or abstractions of reality come to act like direct impressions of reality itself.

This neurodynamic theory may be applied to explain certain of the phenomena seen in various states of inhibition such as sleep or hypnosis, as well as some symptoms of psychopathology. During sleep the second signal system of ideas acts like reality itself and is perceived as the true perception of dreams. While asleep, what one thinks about seems to be really happening. Under hypnosis, with its great ease of suggestibility, the secondary signal acts like the primary or even the unconditional stimulus, and the words or ideas act like reality. As for example in Platanov's(2) work with hypnosis the words "you are drinking" comes to mean the subject is really drinking and a diuresis naturally occurs. Similarly in conversion hysteria and hypochondriasis the idea comes to stand for reality—the idea of a bodily ailment produces the physical symptoms of this ailment.

As for the schizophrenic-like symptoms of mescaline, their description by Stockings (23) and Hoch(11, 12) tend to support this neurodynamic formulation. Hoch states that the contents of the hallucinatory experiences under mescaline were present in a very similar form in dreams and free associations prior to the drug-induced state. The auditory hallucinations usually started as an idea and then the concept is projected and heard from the outside. Occasionally the patient relived actual traumatic experiences. Solomon(20), in describing drug-induced symptoms, says that a phantasy or an illusion, in the process of psychologic dissociation, may appear to the subject as a real object outside himself, and thus constitute an hallucination. Stockings(23) writes that the hallucinatory content was in line with past mental experiences—wish fulfillment fantasies and childhood memories. He describes it as a hypertrophy of the imagination, first appearing in the mind's eye, and then dissociated and appearing as a real object. The thoughts became split off and talked back as voices. Objects seemed to stand out and have a special reference for the subject; instead of being

abstract they became concrete. Sounds seemed very clear and to have a specific meaning for the individual.

Here, again, in hallucinations, the ideas—the second signal system—act like the primary signal system—sensations, perceptions, reality. What was once an idea or daydream becomes under mescaline what seems like reality or an hallucinatory experience.

Normally, ideas that are not reinforced by reality or experience become extinguished. However, in an inhibitory and disorganized state, such as that produced by mescaline, the ideas appear as reality and thus reinforce themselves, becoming fixed delusions, obsessions, and compulsions. To the subject's mind these ideas or secondary signals are accepted as experience or sensations; and so long as they are perceived as primary signals (reality), they do not become extinguished. Further there is a disturbance of thinking in which the individuals lose their ability to generalize—the secondary signal system of words becoming concrete, and acting as direct literal impressions rather than abstractions.

Summary and Conclusion

Mescaline produced an inhibitory state accompanied by a schizokenesis or dissociation of systems. This disharmony was also manifested in that the CS appeared to act in the same manner as the US. On this basis a neurodynamic theory of the mechanism of mescaline's actions is postulated: that under mescaline intoxication and in some mental illnesses, a dissociation of the second and first signaling systems and the unconditional reflexes occurs in which each signaling system acts as if it were the same as the more primitive system on which it is based. The secondary signals—words and ideas—come to act like the primary signals of sensations and direct impressions of reality. This theory may help explain certain psychological phenomena, *e.g.* dreams, hysteria, compulsions, delusions, and hallucinations. While the content of these phenomena depends on the personality of the subject and all the environmental factors that determine this personality, their mechanisms are physiological, regardless of whether one prefers a pathophysiologic or psychogenic etiology. Based on our experimental findings and the work of others, a neurodynamic pathogenesis of the psychological effects of mescaline is described.

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DISCUSSION

Herman C. Denber, M. D. (New York City).—This paper can be studied from 3 vantage points:

(1) The preliminary hypothesis; (2) the experimental data; and (3) the concepts derived therefrom.

There is some confusion regarding the exact role of mescaline in the experimental production of various states of abnormal human behavior. The words "experimental neurosis" and "experimental psychosis" are used interchangeably. These authors state that symptoms of the mescaline-induced state are accompanied by a "lack of insight, and amnesia for the events," and that "high doses produce catatonic reactions." They emphasize the motor components and negativistic behavior of the animals.

In a strict sense, the injection of mescaline in humans produces neither an intoxication, nor a neurosis, nor a psychosis. It is a state of being in which occur behavioral changes ranging from normality to completely disorganized mental states, and from sleep to murderous rage. Use of the words neurosis or psychosis without strict definition only tends in this type of experimental approach to lead to further uncertainty.

The mescaline experience is vividly recalled, for subsequently patients have described it as a "horror or torture chamber," an "emotional brain wash," a "cleansing process," a "purification," and either "an airplane ride" or " a 4-engine transport on the flight line before take-off with all 4 motors going." Of 40 patients who received intravenous injections of mescaline, the majority stated that they would not like to have another. A few requested additional treatments since they felt it helped them in understanding their problems. My own reaction to orally ingested mescaline was that once was enough for science, and twice would definitely be an imposition. The marked insight developed by many patients during the mescaline experience has a beneficial effect upon their illness.

Since the mescaline state in humans is accompanied by autonomic, sensory, motor, thinking, and emotional changes, and since Drs. Bridger and Gantt do not describe much beyond motor and some little emotional changes, it is questionable whether one can really compare the mescaline state in man and dog. Tension and anxiety, almost constant precursors of the mescaline-induced state in humans, seem to have been absent in the dogs. The effect of increasing doses of mescaline upon the conditioned reflex suggests that the mechanism in dogs is not the same as in humans. Variations of dosage in humans does not influence the clinical response. I have seen violent emotional reactions with 0.05 grams and no response with 0.5 grams. Catatonic reactions in humans can be produced by the same dose (0.5 grams) that produces acute rage or sleep. The type of reaction appears to be more a function of the individual's life experience. Negativism and catatonia are unusual in humans, but appear to be the chief response in dogs.

The variability of response to mescaline in humans raises a serious problem as to the applicability of concepts drawn from data on 4 animal subjects of any species. The data of the experiments reported today are not clear-cut. The abolition of conditional responses under mescaline is not total. It may be that in a large number of animals there would be a gradation of responses from complete extinction to no extinction of the conditional reflex. The experimental setting "was designed to prevent stimuli other than the conditional stimuli from interfering with the test." Can formulations derived from this experiment be compared to any life situation with its multiplicity of stimuli, internal and external, playing upon the individual?

The work of Altschule, Bower, and Cook has shown that chlorpromazine hydrochloride effectively suppresses conditioned reflexes in rats. This substance also blocks the mescaline-induced state in humans. One produces abnormal behavior and the other antagonizes abnormal behavior. These 2 mutually antagonistic compounds have the same action; they block the conditioned reflex. The effect of these drugs, and undoubtedly others as well, would therefore seem to be nonspecific.

Emphasis is placed upon the fact that the cardiac component under mescaline in dogs is completely inhibited, while the motor portion of the conditional reflex remains intact. These authors found an inverse split under morphine, although they have not discussed its specific meaning in terms of the psychological concept they propose. Have other drugs been tested to determine if such a split takes place? If morphine produces a dissociation of the emotional and motor components of the conditional reflex, this represents schizokinesis. Since morphine does not produce symptoms of schizophrenia, is it appropriate then to state that "the production of inhibition and schizokinesis under mescaline support the theories" that have been proposed? The emphasis is on a cleavage between emotional, visceral, and motor components. Observation of psychotic patients shows a dissociation in one sphere only—the emotions. Feelings and thoughts are dissociated, for when a schizophrenic patient responds to his anxiety without symptom formation, the result may be disastrous.

To straight-jacket human behavior with its inherent variability and fluidity into signal systems under the guise of being physiologically determined is hardly conducive to further understanding of an already complex subject. Mescaline "produces a disharmony or schizokinesis of the normally coordinated 3 systems of higher nervous activity," only if one considers human behavior in a physiologic Pavlovian frame of reference, forgetting the tremendously complex interplay of environmental forces from birth onward and, as some claim, even before birth.

These authors have not made it clear why the dogs responded to the conditional stimulus as though it were the unconditional one having assumed *a priori* that the basis was physiologic. We who work with humans are more fortunate, for we can ask our patients why they do things. The concretized dichotomy of first and second signal systems is not verifiable clinically—at least not if one adds a psychodynamic frame of reference; which one must do in order to consider the problem of human behavior from a holistic viewpoint. The "verbal concepts or abstractions of reality come to

act like direct impressions of reality," only because one observes the phenomenon of the mescaline-induced state in a straight descriptive sense. The hallucination or delusion is not a concrete realistic phenomenon, no more than is "the idea of bodily ailment producing the physical symptoms of conversion hysteria and hypochondriasis." The delusional symptoms of the mescaline-induced state frequently dissolve when the patient associates the conflict-producing thoughts that have engendered them. As a matter of fact, in a majority of patients, mescaline rather than producing schizokinesis, induces a synthesis of emotions and thoughts precipitating an overwhelming emotional discharge associated with the verbalization of conflicts. The delusion or hallucination then is a mirror of the unconscious. As the patient responds to these "concrete" visions, his anxiety rises to a crescendo, and is then discharged, for he is then looking at himself, a self long hidden.

In this sense, mescaline produces neither a state of inhibition nor a dissociation, but rather a synthesis. Recall of memories takes place on a physiologic base still poorly understood. With intense and unbearable anxiety as a fulcrum, peripheral stimuli assume meaning in conformance with past experiences. Mescaline reduces or dissolves the ego defenses so that feeling is discharged with thought. A circle is then set up with the periphery acting as a trigger.

If this concept is correct, then any agent capable of blocking afferent stimuli should break up the circle and dissolve the mescaline-induced state. Chlorpromazine is such an agent, a fact confirmed recently by Hoch.

While most will agree that the fundamental mechanism of psychic phenomena is physiologically determined, until such time as the genetic, anatomical, biochemical, cultural, and psychodynamic factors are unified, no theory, neurodynamic or otherwise, can be acceptable.

ROLAND FISCHER, PH. D. (Regina, Sask.)—There are 2 points I should like to raise: (1) How far is the mescaline experience specific for that substance? (2) What would be the outcome of the experimental results after the administration of a depot-mescaline, recently synthesized, and which would enable one to perform a "chronic" mescalinization experiment?

In connection with the first question, it is of interest to recall that Chosak in Russia used guinea pigs injected with mescaline. He describes strong passive defense-reactions and cataleptic states (he connects the latter with the ability of mescaline to cause hallucinations). He observed a total disappearance of the artificial as well as of the natural conditioned reflexes and a firm refusal of food. The described disturbances disappeared usually in a few days and the animals appeared again normal. However, even after months he observed a disturbance of the higher nervous activity (phasic, periodic disturbances). The most prolonged were the disturbances of processes of inner inhibition of differentiation and of extinguishing inhibition).

Iwanow-Smolenski mentions the bulbocapnine experiments of Kotljarewski on rats. Experimental catalepsy was produced; first the conditioned (defense) reflexes disappeared, then also the unconditioned ones (food and orientation reflexes) for a few hours. After that the animals behaved normally again, but their conditioned reflexes showed a state of inhibition, first complete, later in phases for 3-5 days, and finally the processes of inner active inhibition (differentiations) were restored. These results appear to corroborate those obtained by Drs. Gantt and Bridger.

Generally all these and other intoxications (caused by staphylococcal, streptococcal, diphtheria, and typhus toxins or as a result of allergic states or tetraethyl lead poisoning) show, as claimed by Iwanow-Smolenski, that the *inhibition phase* which affects first the youngest, artificial C.R.'s, then the natural C.R.'s, goes over to the unconditioned reflexes, and in connection with this then affects the subcortical functions. It is evident that the inhibition retraces the path of evolution from the youngest to the oldest forms of nervous activity. Such reasoning arrived at by experiments producing an experimental or model psychosis also lends some support to my concept which regards schizophrenia as a regressive process of adaptation.

This concept is also supported by our recent findings which help us to regard the metabolic pattern of healthy people during the night as equivalent to the metabolic pattern of certain schizophrenics during the daytime.

The above point of view fits in with the Pavlovian concept of Drs. Bridger and Gantt, according to which, during sleep, mescalinization, or, in certain schizophrenic states, the second signal system of ideas, acts like reality itself.

As to the second point, if we assume that there is a chemical mediation of the schizophrenic syndrome, then it also seems advisable to perform "chronic" mescaline experiments. Jatzkewitz in München recently synthesized a depot-mescaline which is chemically tied to polyvinylpyrrolidon; this complex provides, after a single administration, a steady daily dosage of very small amounts of mescaline into the blood stream for about 3 weeks. It would be interesting to see the outcome of the experimental results described by Drs. Gantt and Bridger after repeated administration of this depot-mescaline. It might be that the organism then would respond with the formation of an adaptive enzyme (system) able to metabolize the drug. Such experiments might serve as a model for the increased resistance toward various drugs of the chronic schizophrenic.

A final point—there are many reasons which make me believe that the intact mescaline molecule is not, in itself, an active substance.

Let us hope that the present renaissance of mescaline research will contribute to the elucidation of this and other related intriguing problems.